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A New and Versatile Synthesis of 1,3-Dioxan-5-yl-pyrimidine and Purine Nucleoside Analogues

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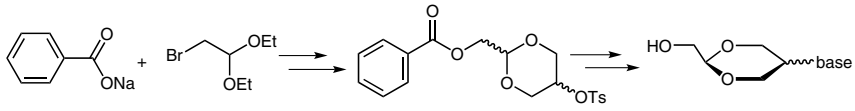

- all 1,3-dioxane based nucleoside analogues were obtained
- both *trans* and *cis* diastereoisomers were isolated and structurally characterized

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Abstract 1,3-Dioxan-5-yl pyrimidine and purine nucleoside analogues were prepared following a new and versatile synthetic strategy. These analogues were synthesized via nucleophilic addition of the selected nucleobase to a 1,3-dioxane scaffold that presents an appropriate leaving group in position 5. In particular *cis* and *trans* isomers of purine/pyrimidine nucleosides and their halogenated homologues were obtained. NMR experiments, carried out on the *cis* isomers, led to assignment of an equatorial orientation to the 2-hydroxymethyl group and axial orientation to the nucleobase in position 5 of the 1,3-dioxane. The *trans* isomers showed a diequatorial orientation of these groups. These assignments were confirmed by X-ray crystallographic studies.

Key words nucleosides, 1,3-dioxane, purines, pyrimidines, antiviral

The synthesis and biological evaluation of nucleoside analogues have been a very active research area for a number of years.[1,2] Among them, a well-known class of molecules endowed with antiviral or anticancer activity was obtained by replacing the 2-deoxyribose moiety with a 1,3-dioxolane[3,4] or 1,3-oxathiolane ring.[5,6] Based on the results reported, we focused part of our research on the synthesis of nucleoside analogues having these novel sugar-replacing rings. Furthermore, with the aim to investigate the properties of higher homologues of the 1,3-dioxolane-based nucleosides, 1,3-dioxane analogues were also considered (Figure 1).

Although 1,3-dioxan-5-yl pyrimidines were previously reported as potential anti-HIV nucleoside alike compounds,[7,8] we felt that the true value of a structural modification concerning the sugar portion would only be completely revealed when all nucleoside analogues were produced and evaluated. This consideration is supported by the case of 1,3-oxathiolane-based nucleosides in which only the cytosine analogue showed a good antiviral (i.e., HIV, HBV) potency and selectivity.[5] Supported by this evidence, we developed a novel synthetic approach to obtain the corresponding purine derivatives. Unlike the previously reported methods, the synthetic strategy presented herein allowed us to isolate and fully characterize both *cis* and *trans* isomers of all targeted derivatives. The 1,3-dioxane-based nucleosides were obtained by reacting each purine and pyrimidine base with a key intermediate in the last step of the synthetic pathway. This strategy avoids the expensive and time-consuming Mitsunobu-type condensation of bis-1,3-trityloxy-2-propanol with each nucleobase in the first step of the synthetic path.[7,8] In addition, it overcomes the demanding separation of the *cis*/*trans* diastereoisomers to be performed on the precious and hard-to-handle nucleoside mixture. Moreover, the Mitsunobu reaction cannot be applied in the case of purines due to their poor solubility in the suitable reaction solvents. At present, 1,3-dioxan-5-yl-purine nucleosides have never been isolated and characterized. In this work we developed a different synthetic approach in order to obtain a large variety of *cis*- and *trans*-pyrimidine/purine nucleoside analogues by using a com-

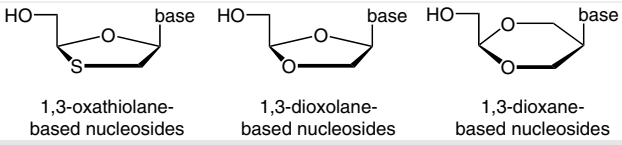


Figure 1

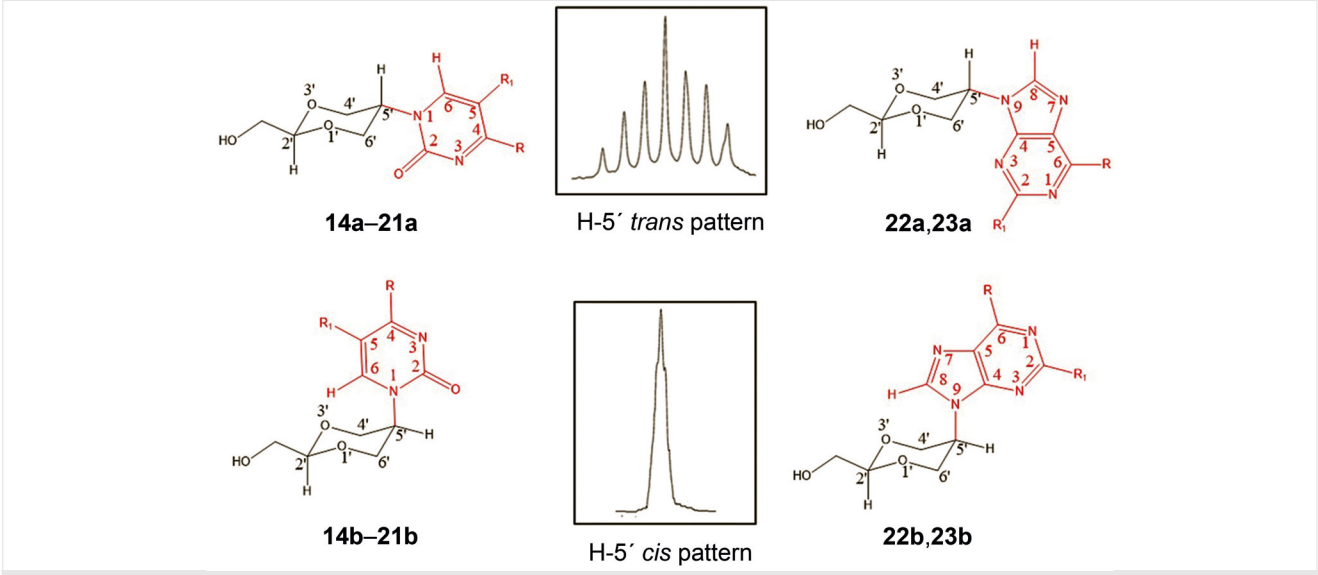


Figure 2 Upper: *trans* isomers of 1,3-dioxane-based nucleoside analogues **14a**–**23a** and ^{1}H NMR signal of H-5′. Lower: *cis* isomers **14b**–**23b** and ^{1}H NMR signal of H-5′.

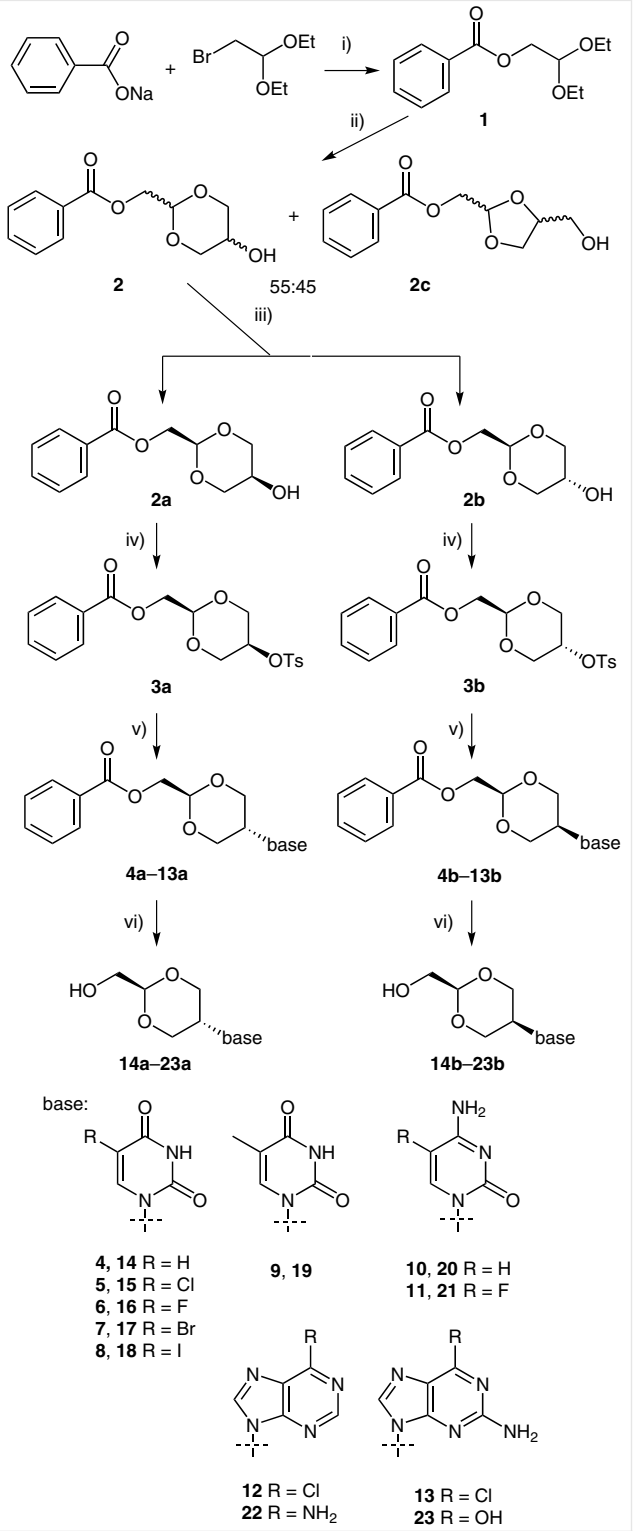
mon intermediate (Scheme 1). Diethyl acetal **1**,[17] required as starting material, was prepared from sodium benzoate and bromoacetaldehyde diethyl acetal. Synthesis of the 1,3-dioxane ring was accomplished by Lewis acid mediated condensation of **1** with glycerol to give compound **2**.[9,18] The reaction proceeds without stereoselectivity and regioselectivity preferences, giving *cis* (**2a**)[19] and *trans* (**2b**)[20] isomers in comparable yields as well as their corresponding 1,3-dioxolane isomers. The molar ratio of 1,3-dioxane/1,3-dioxolane *cis*,*trans*-diastereoisomeric mixture was 55:45. However, due to the marked difference in polarity, the single diastereoisomers of **2** were easily separated by flash column chromatography and obtained in high purity free from their lower homologues (1,3-dioxolanes). Treatment of **2a** and **2b** with *p*-toluenesulfonyl chloride gave the key intermediates **3a** and **3b**,[21] respectively. Nucleophilic displacement of the tosyl group by the selected nucleobase produced an inversion of the configuration at C-5 of the 1,3-dioxane and furnished *trans* (**4a**–**13a**) and *cis* isomers (**4b**–**13b**),[22–24] respectively, of the desired nucleosides. Deprotection of the hydroxyl group in position 2 of the 1,3-dioxane with NH_3–H_2O and the subsequent crystallization gave the final pyrimidine nucleosides as pure *trans* (**14a**–**21a**) or *cis* diastereoisomers (**14b**–**21b**; Scheme 1,Table 1).[25]

The desired adenine analogues **22a** and **22b**[26] were obtained by treatment of the parent compounds **12a** and **12b** with saturated NH_3–H_2O, in a reactor at 100 °C. Compounds **13a** and **13b** were transformed into the final guanine nucleosides **23a** and **23b**[27] by heating at 100 °C in the presence of aqueous NaOH–methanol solution (Scheme 1).

Stereochemical and conformational assignments were based on NMR studies. The relative chemical shifts of the H-5′ (1,3-dioxane) and H-6 (pyrimidine) or H-8 (purine) were

Table 1 Synthesized Compounds[28]

Nucleoside	Nucleobase	Nucleobase abbreviation
14a	uracil	U
14b	uracil	U
15a	5-chlorouracil	5ClU
15b	5-chlorouracil	5ClU
16a	5-fluorouracil	5FU
16b	5-fluorouracil	5FU
17a	5-bromouracil	5BrU
17b	5-bromouracil	5BrU
18a	5-iodouracil	5IU
18b	5-iodouracil	5IU
19a	thymine	T
19b	thymine	T
20a	cytosine	C
20b	cytosine	C
21a	5-fluorocytosine	5FC
21b	5-fluorocytosine	5FC
22a	adenine	A
22b	adenine	A
23a	guanine	G
23b	guanine	G



Scheme 1 *Reagents and conditions*: i) 18-crown-6, DMF, 160 °C, 6 h; (ii) $CoCl_2$, TMSCl, glycerol, MeCN, r.t., 0.1 h; iii) flash column chromatography (cyclohexane–EtOAc, 70:30); iv) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 12 h; v) K_2CO_3, selected pyrimidine or purine, 18-crown-6, DMF, 160 °C, 24 h; vi) NH_3–H_2O, r.t., 5 h (**4a**–**11a** and **4b**–**11b**) or NH_3–H_2O, 100 °C, 12 h (**12a**,**b**) or 40% NaOH–MeOH, 100 °C, 5 h (**13a**,**b**).

taken into account to assign the *cis*/*trans* configurations to all final compounds **14**–**23** (Figure 2 and Table 2). In particular, the H-5′ signal of the *trans* isomers appears downfield with respect to that of the corresponding *cis* isomers. This result is probably due to the deshielding effect of the 1,3-dioxane oxygen atoms, suggesting an axial orientation of H-5′. Alternatively, in the *cis* isomers the H-5′ proton is arranged equatorially so that the nucleobase presents an axial orientation. The deshielding effect of the oxygen atoms is exerted also on H-6 of the pyrimidine or on H-8 of the purine. In particular, when the base is axially oriented, as in the *cis* isomers, the signal of these protons falls at lower field with respect to that of the corresponding *trans* isomer. Moreover, the pattern of all H-5′ protons unambiguously confirmed that in all *cis* isomers the nucleobase is axially oriented while in *trans* isomers the base has equatorial orientation (Figure 2). In fact, for the *cis* isomers, the H-5′ peak is a broadened singlet with two small coupling constants. This evidence is in good agreement with an equatorial orientation of this proton when 2′,5′-disubstituted 1,3-dioxanes show a C-2′,C-5′ *cis* configuration. By contrast, the H-5′ signal of the *trans* isomers appears as a defined multiplet, with two large coupling constants that indicate its axial ori-

Table 2 ^{1}H NMR Chemical Shifts (multiplicity) of H-5′, H-6, or H-8 of the 1,3-Dioxane-Based Nucleoside Analogues **14**–**23**[a]

Compound	Base	Isomer	H-5′	H-6[b] or H-8[c]
14a	U	*trans*	4.32–4.51 (m)	7.72 (d)
14b	U	*cis*	4.29 (br s)	8.15 (d)
15a	5ClU	*trans*	4.41–4.52 (m)	8.16 (s)
15b	5ClU	*cis*	4.31 (br s)	8.47 (s)
16a	5FU	*trans*	4.39–4.49(m)	8.11 (d)
16b	5FU	*cis*	4.30 (br s)	8.37 (d)
17a	5BrU	*trans*	4.39–4.49 (m)	8.20 (s)
17b	5BrU	*cis*	4.32 (br s)	8.45 (s)
18a	5IU	*trans*	4.42–4.58 (m)	8.22 (s)
18b	5IU	*cis*	4.33 (br s)	8.61 (s)
19a	T	*trans*	4.41–4.58 (m)	7.62 (s)
19b	T	*cis*	4.31 (br s)	8.04 (s)
20a	C	*trans*	4.43–4.59 (m)	7.61 (d)
20b	C	*cis*	4.30 (br s)	8.11 (d)
21a	5FC	*trans*	4.45–4.61 (m)	8.03 (d)
21b	5FC	*cis*	4.30 (br s)	8.28 (d)
22a	A	*trans*	4.61–4.82 (m)	8.21 (s)
22b	A	*cis*	4.51 (br s)	8.40 (s)
23a	G	*trans*	4.31–4.50 (m)	7.63 (s)
23b	G	*cis*	4.29 (br s)	7.88 (s)

[a] ^{1}H NMR: 400 MHz, DMSO-d_6 as solvent, TMS as internal reference.
[b] Pyrimidine derivatives.
[c] Purine derivatives.

entation. These results were confirmed by ^{1}H NMR studies on 2′,5′-disubstituted 1,3-dioxane analogues.[7,8,10] The NMR structural elucidations were further supported by X-ray crystallographic studies. The crystals of **22b**, obtained from aqueous solution, were analyzed by single-crystal X-ray diffraction at room temperature. The crystals were monoclinic (space group $P2_1/c$) with four molecules per unit cell. Bond lengths and angles are unexceptional, as compared with those found in cyclohexyl[11] and pyranosyl[12] derivatives of adenine. The 1,3-dioxane ring adopts a chair conformation, with the adenine and hydroxymethyl groups in axial and equatorial positions, respectively (Figure 3).

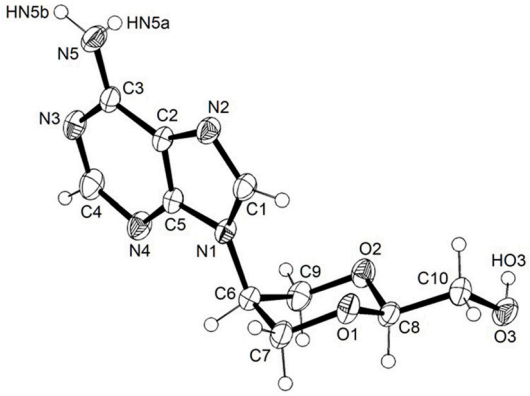


Figure 3 Partially labeled ORTEP-3 plot of **22b**, with displacement ellipsoids at 40% probability level and H atoms drawn as spheres with arbitrary radius.[14] Only H atoms bound to heteroatoms are labeled.

The purine base is in the *anti* orientation with respect to the 1,3-dioxane ring, as shown by the torsion angle C7–C6–N1–C5, –151.31(7)°. The molecular structure is remarkably similar to that of *trans*-9-(2-ethoxy-1,3-dioxan-5-yl)adenine, which, however, features the ethoxy substituent in axial position.[13]

In the crystal lattice, complementary donor–acceptor interactions link molecules in chains that run parallel to the *c* axis. The hydroxyl oxygen atom O3 is hydrogen-bonded to the imidazole nitrogen atom N2 of a neighboring molecule [O3–HO3···N2 2.7759(11) Å]. In turn, the exocyclic amino group of the latter acts as a hydrogen donor towards one of the 1,3-dioxane ring oxygens [N5–HN5a···O2 3.0265(11) Å]. These chains are connected to each other via a third hydrogen bond that involves the remaining amino hydrogen and the pyrimidine nitrogen atom N3 [N5–HN5b···N3 3.0645(10) Å]. The crystal structure is further stabilized by short C–H···O contacts and base-stacking interactions.

All synthesized nucleosides **14**–**23** were evaluated for their potential activity against a variety of viruses following the previously described procedures.[15] None of the compounds showed significant antiviral activity against human immunodeficiency virus type 1 and 2 (HIV-1, HIV-2), herpes simplex virus type 1 and 2 (HSV-1, HSV-2), *vaccinia* virus and *vescicular stomatitis* virus (VSV) in infected MT-4 (for HIV) or HEL (other viruses) cell cultures. Moreover no microscopically visible cytotoxicity was observed at the highest concentrations tested (i.e., 200 µM) of all compounds. The compounds were also evaluated for cytotoxic effects towards several human cancer cell lines such as HCT116 (colon), A549 (lung), SNU638 (stomach), PC3 (prostate), SK-Hep-1 (liver), using sulforhodamine B (SRB) protein staining method.[16] None of the tested compounds showed significant antitumor activity, with an EC_{50} value > 100 µM.

In summary, a new and versatile synthesis of achiral 1,3-dioxan-5-yl-based nucleosides (pyrimidin-1-yl/purin-9-yl) has been developed. This synthetic strategy allows both *cis* and *trans* diastereoisomers of all purine and pyrimidine analogues to be obtained. Furthermore, 1,3-dioxan-5-yl purines were isolated and structurally characterized for the first time. None of the compounds possesses significant antiviral and antitumor activity in the biological assays performed. Further or different modifications have to be introduced to unlock the antiviral/antitumor activity. However, this synthetic approach may represent a valuable tool for obtaining new analogues of this class of compounds.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380112.

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(17) **Benzoyloxyacetaldehyde Diethyl Acetal (1)**

Potassium benzoate (125.2 mmol, 20.0 g) was added to a solution of bromoacetaldehyde diethyl acetal (160.0 mmol, 24.4 mL) and 18-crown-6 ether (catalytic amount) in anhydrous DMF (25 mL), and the mixture was refluxed for 6 h. Then, after cooling to r.t., H_2O was added, and the mixture was extracted three times with EtOAc. The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated under vacuum. The residue was dried azeotropically with toluene to give benzoyloxyacetaldehyde diethyl acetal (24.72 g, 104.0 mmol, 83%). This product was used in the next step without further purification.

Dark oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 6 H, 2 × CH_3), 3.54–3.68 (m, 2 H, CH_2CH_3), 3.68–3.80 (m, 2 H, CH_2CH_3), 4.35 (d, *J* = 5.4 Hz, 2 H, CH_2OCO), 4.84 (t, *J* = 5.4 Hz, 1 H, CH), 7.43 (dd, *J* = 7.6, 7.7 Hz, 2 H, CH-3, CH-5 Ph), 7.55 (t, *J* = 7.6 Hz, 1 H, CH-4 Ph), 8.05 (d, *J* = 7.7 Hz, 2 H, CH-2, CH-6 Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0 (2 CH_3), 62.2 (2 CH_2), 64.1 (CH_2OCO), 99.4 (CH), 128.1 (C-3, C-5 Ph), 129.4 (C-2, C-6 Ph), 129.7 (C-1 Ph), 132.8 (C-4 Ph), 166.0 (CO). HRMS-APCI: *m/z* calcd for $C_{13}H_{19}O_4^+$ $[M + H]^+$: 239.1278; found: 239.1280.

(18) **(5-Hydroxy-1,3-dioxan-2-yl)methyl Benzoate (2)**

To a solution of $CoCl_2$ (9.7 g, 75.0 mmol) in anhydrous MeCN (100 mL), benzoyloxyacetaldehyde diethyl acetal (**1**, 33.3 g, 140.0 mmol), TMSCl (19.0 mL, 149.0 mmol), and glycerol (19.3 mL, 265.0 mmol) were added at r.t. under stirring. After 12 h the reaction was stopped, the mixture was extracted three times with EtOAc, and the extracts were collected and washed with $NaHCO_3$ (5%). The organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated under vacuum to give an oily residue. Purification and separation of two diastereoisomers **2a** and **2b** was achieved by flash column chromatography (cyclohexane–ethyl acetate, 70:30): 5.00 g of *cis* isomer **2a** (21.0 mmol, 15%), 5.34 g of *trans* isomer **2b** (22.4 mmol, 16%), and 10.0 g of [4-(hydroxymethyl)-1,3-dioxolan-2-yl]methyl benzoate (**2c**, 42.0 mmol, 30%) as an inseparable *cis*/*trans* diastereoisomeric mixture (50:50) were obtained. Molar ratio 1,3-dioxanes/1,3-dioxolanes = 55:45.

(19) ***cis*-(5-Hydroxy-1,3-dioxan-2-yl)methyl Benzoate (2a)**

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (br s, 1 H, OH), 3.52–3.61 (m, 1 H, CH-5 diox), 3.90–4.01 (m, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.04–4.13 (m, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.40 (d, *J* = 4.6 Hz, 2 H, CH_2O), 4.96 (t, *J* = 4.6 Hz, 1 H, CH-2 diox), 7.44 (dd, 2 H, *J* = 7.4, 7.8 Hz, CH-3, CH-5 Ph), 7.57 (t, 1 H, *J* = 7.4 Hz, CH-4 Ph), 8.01 (d, 2 H, *J* = 7.8 Hz, CH-2, CH-6 Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.0 (C-5 diox), 64.9 (CH_2OCO), 71.9 (C-4, C-6 diox), 98.9 (C-2 diox), 128.5 (C-3, C-5 Ph), 129.6 (C-1 Ph), 129.7 (C-2, C-6 Ph), 133.2 (C-4 Ph), 166.2 (CO). HRMS-APCI: *m/z* calcd for $C_{12}H_{15}O_5^+$ $[M + H]^+$: 239.0914; found: 239.0917.

(20) ***trans*-(5-Hydroxy-1,3-dioxan-2-yl)methyl Benzoate (2b)**

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.02 (br s, 1 H, OH), 3.42 (dd, *J* = 10.4, 10.8 Hz, 2 H, CH-4_{ax}, CH-6_{ax} diox), 3.81–3.91 (m, 1 H, CH-5 diox), 4.22 (dd, *J* = 4.9, 10.4 Hz, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.35 (d, *J* = 4.6 Hz, 2 H, CH_2O), 4.78 (t, *J* = 4.6 Hz, 1 H, CH-2 diox), 7.43 (dd, 2 H, *J* = 7.2, 7.8 Hz, CH-3, CH-5 Ph), 7.55 (t, 1 H, *J* = 7.2 Hz, CH-4 Ph), 8.04 (d, 2 H, *J* = 7.8 Hz, CH-2, CH-6 Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.7 (C-5 diox), 64.4 (CH_2OCO), 70.8 (C-4, C-6 diox), 97.8 (C-2 diox), 128.2 (C-3, C-5 Ph), 129.2 (C-1 Ph), 129.5 (C-2, C-6 Ph), 133.1 (C-4 Ph), 166.1 (CO). HRMS-APCI: *m/z* calcd for $C_{12}H_{15}O_5^+$ $[M + H]^+$: 239.0914; found: 239.0915.

(21) ***trans*-[5-(Tosyloxy)-1,3-dioxan-2-yl]methyl Benzoate (3b)**

p-Toluenesulfonyl chloride (1.20 g, 6.3 mmol) was added at 0 °C to a solution of **2b** (1.0 g, 4.2 mmol), Et_3N (8.4 mmol, 1.17 mL) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 12 h. Ice and H_2O were added, and the mixture was extracted with CH_2Cl_2. The organic extracts were collected and dried (Na_2SO_4). Crystallization from EtOAc–cyclohexane afforded the desired compound (0.86 g, 2.2 mmol, 52%).

White solid; mp 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 3.57 (dd, *J* = 10.4, 11.3 Hz, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.14 (dd, *J* = 5.3, 11.3 Hz, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.32 (d, *J* = 4.6 Hz, 2 H, CH_2O), 4.45–4.58 (m, 1 H, CH-5 diox), 4.78 (t, *J* = 4.5 Hz, 1 H, CH-2 diox), 7.31–7.45 (m, 2 H, CH-2, CH-6 Ph), 7.43–7.56 (m, 2 H, CH-3, CH-5 Ph), 7.58–7.64 (m, 1 H, CH-4 Ph), 7.81 (d, *J* = 8.4 Hz, 2 H, CH-3, CH-5 Ts), 8.04 (d, *J* = 8.4 Hz, 2 H, CH-2, CH-6 Ts). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (CH_3), 63.9 (CH_2OCO), 67.5 (C-5 diox), 67.9 (C-4, C-6 diox), 98.1 (C-2 diox), 127.6 (C-3, C-5 Ts), 128.1 (C-3, C-5 Ph), 129.5 (C-2, C-6 Ts), 129.2 (C-1 Ph), 129.9 (C-2, C-6 Ph), 133.4 (C-4 Ph), 133.7 (C-1 Ts), 145.3 (C-4 Ts), (165.8 (CO). HRMS-APCI: *m/z* calcd for $C_{19}H_{21}O_7S^+$ $[M + H]^+$: 393.1003; found: 393.1006.

(22) ***cis*-{5-[5-Chloro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-1,3-dioxan-2-yl}methyl Benzoate (5b)**

To a suspension of 5-chlorouracil (1.2 mmol) and K_2CO_3 (1.2 mmol), in anhydrous DMF (10 mL), was added portionwise, under nitrogen, the tosylated compound **3b** (1 mmol) and 18-crown-6 (catalytic amount). The resulting mixture was stirred and heated to reflux for 24 h. After cooling to r.t. the mixture was concentrated under vacuum. The residue was partitioned between EtOAc and H_2O. The organic layer was separated, and the aqueous phase was extracted with EtOAc. The extracts were

combined, washed with H_2O, and dried (Na_2SO_4). The suspension was filtered and the solvent evaporated under vacuum. The residue obtained was purified by flash chromatography to yield the desired compound (0.046 g, 0.125 mmol, 12%).
Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19–4.37 (m, 4 H, CH_2-4, CH_2-6 diox), 4.50 (br s, 1 H, CH-5 diox), 4.53 (d, *J* = 3.8 Hz, 2 H, CH_2O), 5.11 (t, *J* = 3.8 Hz, CH-2 diox), 7.53 (dd, *J* = 7.5, 8.0 Hz, 2 H, CH-3, CH-5 Ph), 7.69 (dd, *J* = 1.3, 7.5 Hz, 1 H, CH-4 Ph), 7.94 (dd, *J* = 1.3, 8.0 Hz, 2 H, CH-2, CH-6 Ph), 8.65 (s, 1 H, CH-6 uracil). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.5 (C-5 diox), 64.0 (*C*H_2OCO), 68.5 (C-4, C-6 diox), 99.0 (C-2 diox), 108.7 (C-5 uracil), 128.3 (C-3, C-5 Ph), 129.6 (C-2, C-6 Ph), 129.9 (C-1 Ph), 133.2 (C-4 Ph), 139.6 (C-6 uracil), 149.2 (C-2 uracil), 157.8 (C-4 uracil), 166.1 (CO). ESI-HRMS: *m/z* calcd for $C_{16}H_{16}ClN_2O_6^+$ [M + H]$^+$: 367.0691; found: 367.0692.

(23) ***cis*-[5-(6-Chloro-9*H*-purin-9-yl)-1,3-dioxan-2-yl]methyl Benzoate (12b)**
The compound was obtained from **3b** and 6-chloropurine, following the procedure described for **5b** (0.059 g, 0.158 mmol, 15%).
Dark-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.38 (m, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.39–4.46 (m, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.49 (d, *J* = 4.3 Hz, 2 H, CH_2O), 4.82 (br s, 1 H, CH-5 diox), 5.21 (t, *J* = 4.3 Hz, 1 H, CH-2 diox), 7.48 (dd, *J* = 7.5, 7.8 Hz, 2 H, CH-3, CH-5 Ph), 7.60 (dd, *J* = 1.2, 7.5 Hz, 1 H, CH-4 Ph), 8.07 (dd, *J* = 1.2, 7.8 Hz, 2 H, CH-2, CH-6 Ph), 8.73 (s, 1 H, CH-2 purine), 8.92 (s, 1 H, CH-8 purine). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.5 (C-5 diox), 64.6 (*C*H_2OCO), 69.0 (C-4, C-6 diox), 99.4 (C-2 diox), 128.5 (C-3, C-5 Ph), 129.3 (C-1 Ph), 129.8 (C-2, C-6 Ph), 131.0 (C-5 purine), 133.5 (C-4 Ph), 145.4 (C-8 purine), 151.1 (C-4 purine), 151.5 (C-6 purine), 151.8 (C-2 purine), 166.1 (CO). ESI-HRMS: *m/z* calcd for $C_{17}H_{16}ClN_4O_4^+$ [M + H]$^+$: 375.0855; found: 375.0862.

(24) ***cis*-[5-(2-Amino-6-chloro-9*H*-purin-9-yl)-1,3-dioxan-2-yl]methyl Benzoate (13b)**
The compound was obtained from **3b** and 6-chloro-2-aminopurine, following the procedure described for **5b** (0.063 g, 0.162 mmol, 16%).
Dark-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.44 (m, 4 H, CH_2-4, CH_2-6 diox), 4.50 (d, *J* = 4.2 Hz, 2 H, CH_2O), 4.69 (br s, 1 H, CH-5 diox), 5.05 (br s, 2 H, NH_2), 5.18 (t, *J* = 4.2 Hz, 1 H, CH-2 diox), 7.51 (dd, *J* = 7.4, 7.8 Hz, 2 H, CH-3, CH-5 Ph), 7.62 (t, *J* = 7.4 Hz, 1 H, CH-4 Ph), 8.09 (d, *J* = 7.8 Hz, 2 H, CH-2, CH-6 Ph), 8.77 (s, 1 H, CH-8 purine). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.8 (C-5 diox), 64.4 (*C*H_2OCO), 68.8 (C-4, C-6 diox), 99.5 (C-2 diox), 128.9 (C-3, C-5 Ph), 129.4 (C-1 Ph), 129.9 (C-2, C-6 Ph), 130.8 (C-5 purine), 133.5 (C-4 Ph), 139.6 (C-8 purine), 151.5 (C-6 purine), 152.7 (C-4 purine), 159.1 (C-2 purine), 166.0 (CO). ESI-HRMS: *m/z* calcd for $C_{17}H_{17}ClN_5O_4^+$ [M + H]$^+$: 390.0964; found: 390.0969.

(25) ***cis*-5-Chloro-1-[2-(hydroxymethyl)-1,3-dioxan-5-yl]pyrimidine-2,4(1*H*,3*H*)-dione (15b)**
Compound **5b** (0.046 g, 0.125 mmol) was dissolved in concentrated aq NH_3 (15 mL) and stirred for 5 h in a Pyrex pressure tube. After evaporation of the solvent under vacuum, the residue was crystallized from MeOH–Et_2O to give the desired compound (0.026 g, 0.099 mmol, 79%).
White solid; mp 207–209 °C. ^{1}H NMR (400 MHz, DMSO): δ = 3.34–3.47 (m, 2 H, *C*H_2OH), 4.01–4.12 (m, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.13–4.21 (m, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.31 (br s, 1 H, CH-5 diox), 4.71 (t, *J* = 4.1 Hz, 1 H, CH-2 diox), 4.95 (t, *J* = 6.0 Hz, 1 H, OH), 8.47 (s, 1 H, CH-6 uracil), 11.30 (br s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO): δ = 47.5 (C-5 diox), 62.4 (CH_2OH), 68.0 (C-4, C-6 diox), 100.6 (C-2 diox), 108.3 (C-5 uracil), 141.2 (C-6 uracil), 160.3 (C-2 uracil), 163.4 (C-4 uracil). Anal. Calcd for $C_9H_{11}ClN_2O_5$: C, 41.16; H, 4.22; N, 10.67. Found: C, 41.05; H, 4.14; N, 10.41. ESI-HRMS: *m/z* calcd for $C_9H_{12}ClN_2O_5^+$ [M + H]$^+$: 263.0429; found: 263.0428..

(26) ***cis*-[5-(6-Amino-9*H*-purin-9-yl)-1,3-dioxan-2-yl]methanol (22b)**
Compound **12b** (0.055 g, 0.147 mmol) was dissolved in concentrated aq NH_3 (15 mL) and placed in a reactor at 100 °C for 12 h. After solvent evaporation under vacuum, the residue was crystallized from MeOH–Et_2O to give the desired compound (0.025 g, 0.100 mmol, 68%).
Yellow solid; mp 255–257 °C. ^{1}H NMR (400 MHz, DMSO): δ = 3.47 (dd, 2 H, *J* = 4.0, 6.2 Hz, *C*H_2O), 4.02–4.16 (m, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.18–4.32 (m, 2 H, CH-4_{eq}, CH-6_{eq} diox), 4.51 (br s, 1 H, CH-5 diox), 4.69 (t, *J* = 4.0 Hz, 1 H, CH-2 diox), 4.90 (t, *J* = 6.2 Hz, 1 H, OH), 7.17 (br s, 2 H, NH_2), 8.08 (s, 1 H, CH-2 purine), 8.40 (s, 1 H, CH-8 purine). ^{13}C NMR (100 MHz, DMSO): δ = 49.3 (C-5 diox), 62.5 (CH_2OH), 67.9 (C-4, C-6 diox), 101.3 (C-2 diox), 118.9 (C-5 purine), 139.4 (C-8 purine), 149.5 (C-4 purine), 153.0 (C-2 purine), 156.3 (C-6 purine). Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.87. Found: C, 47.86; H, 5.44; N, 28.03. ESI-HRMS: *m/z* calcd for $C_{10}H_{14}N_5O_3^+$ [M + H]$^+$: 252.1091; found: 252.1093.

(27) ***cis*-2-Amino-9-[2-(hydroxymethyl)-1,3-dioxan-5-yl]-1*H*-purin-6(9*H*)-one (23b)**
Compound **13b** (0.060 g, 0.154 mmol) was dissolved in MeOH and 40% NaOH aq solution was added. The reaction mixture was heated to reflux at 100 °C for 5 h, after which the solvent was removed under vacuum. The solid residue was then dissolved in DMF, and insoluble material was removed by filtration. The DMF was evaporated under vacuum to give a black oil. Crystallization from MeOH–Et_2O afforded the desired compound (0.035 g, 0.131 mmol, 85%).
Yellow solid; mp 280–282 °C. ^{1}H NMR (400 MHz, DMSO): δ = 3.41–3.49 (m, 2 H, *C*H_2OH), 4.01–4.13 (m, 2 H, CH-4_{ax}, CH-6_{ax} diox), 4.19–4.31 (m, 3 H, CH-5, CH-4_{eq}, CH-6_{eq} diox), 4.69 (t, *J* = 4.2 Hz, 1 H, CH-2 diox), 4.81–4.92 (m, 1 H, OH), 6.52 (br s, 2 H, NH_2), 7.88 (s, 1 H, CH-8 purine). ^{13}C NMR (100 MHz, DMSO): δ = 49.3 (C-5 diox), 62.5 (CH_2OH), 67.9 (C-4, C-6 diox), 101.3 (C-2 diox), 116.6 (C-5 purine), 134.9 (C-8 purine), 151.3 (C-4 purine), 155.8 (C-6 purine), 158.6 (C-2 purine). Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.97; H, 5.16; N, 26.49. ESI-HRMS: *m/z* calcd for $C_{10}H_{14}N_5O_4^+$ [M + H]$^+$: 268.1040; found: 268.1041.

(28) Experimental procedures and analytical data of all compounds reported in this work can be found in the Supporting Information.